

REMARKS

Consideration of the application and the amendments above is respectfully requested.

Claims 1-10 and 16-20 were pending in the present application. Claims 1-10 are objected to. Claims 16-20 are rejected. Claims 3 and 11 – 19 have been canceled. Claims 1, 2, 4, 5, 7, 8 and 9 have been amended. New Claim 21 was added. Claims 1, 2, 4 – 10, 20 and 21 are currently pending.

Applicants have canceled Claims 3 and 11- 19 without prejudice to pursuing the subject matter of these canceled claims in a divisional application.

Applicants have amended Claims 1, 2, 4, 5 and 9 to comply with the finalized restriction requirement by defining R¹ and R⁵ as hydrogen, R² as -CH₃, Ar¹ as phenyl, Ar² as phenyl, Ar³ as phenyl, and X as -CH₂-. Support for substituting phenyl for the term "aryl" in these claims is provided in Claims 4 and 5, and on page 10, lines 7-8 of the specification. Support for substituting -CH₂- and -CH₃ for C₁₋₄alkyl in the definitions of X and R² is found in Claim 2 and on page 9, lines 21-24 of the specification.

Claim 1 has also been amended to delete an extra "and" in the definition of R⁴. Claim 4 has also been amended to depend from Claim 1 instead of from cancelled Claim 3.

Claims 7 and 8 have been amended to insert numbers to identify each of the compounds claimed. Claim 8 has been amended to delete compounds 21 and 49 wherein Ar³ is cyclohexyl to comply with the restriction requirement. Claim 8 was further amended by renumbering the compounds after the deletion of compounds 21 and 49.

New Claim 21 has been added directed to a method of treating obesity by administering a compound of Claim 1. Support for Claim 21 can be found in original Claims 16-19 and on page 2, lines 23-25 of the specification.

No new matter has been added to the above-captioned application by the amendments.

INTERVIEW SUMMARY

The Examiner interviewed the Applicant on July 20, 2007 and has provided an interview summary as part of the Office Action of August 2, 2007. The Examiner's summary of the interview, as enclosed with this office action, states:

1. The Examiner proposed that the product claims would be allowable if all of the claims were amended to within the scope of the elected group. The applicant's attorney, Baerbel Brown asked that the method claims be rejoined, and the Examiner indicated he would check with his supervisor. The interview ended without agreement concerning rejoining the method claims.

2. After the interview, the Examiner determined that method claims 16-20 would have a 112 first paragraph issue. The Examiner issued this office action on the Applicant's request to give the applicant an opportunity to provide support for the method claims.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH
FOR LACK OF ENABLEMENT

The Examiner rejected Claims 16-20 under 35 USC 112, first as failing to comply with the written description requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Applicants respectfully disagree. Applicants submit that the specification does give guidance and examples sufficient for treating disorders, including obesity and obesity related disorders. Biological Example 1 on page 116, lines 1-19 of the specification discloses a CB-1 binding assay to determine IC50 values, and the specification states that the exemplified compounds of formula I have and IC50 less than or equal to 2 micromolar. Biological Example 2 on page 116, line 20 to page 117, line 3 of the specification discloses a CB-1 functional assay to determine EC50 values, and the specification states that the Cb-1 antagonists/inverse agonists of the present invention generally have IC50 values less than 1 micromolar. Biological Examples 3 (food intake reduction) and 4 (weight reduction) on page 117 of the specification further disclose how to test and use the compounds of the present invention. The specification provides a statement of the utility of the claimed compounds on page 12, line 35 to page 13, line 25. The specification discloses that the compounds of the present invention are useful to treat and prevent the diseases claimed in Claims 16-20, including how to treat and prevent obesity as claimed in Claim 20 and in new Claim 21. The utility of cannabinoid antagonists/inverse agonists to treat obesity is further disclosed in the literature references listed in the specification on page 1. The specification further teaches how to use the claimed compounds including a detailed description of routes of

administration and dosages. Specifically, the dosage ranges of 0.001 mg/kg to 100 mg/kg of body weight are listed on page 14, lines 24-28; and the routes of administration for the compounds of the present invention are recited as "oral, rectal, topical, parenteral, ocular, pulmonary, nasal" on page 15, lines 14-18.

Applicants submit that the specification sufficiently describes how the compounds of the present invention can be used and sufficiently describes how and in what dosage the compounds of the present invention can be administered.

The Examiner stated that the art as discussed by the references above, particularly with regards to treating obesity and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Applicants submit that the specification provides guidance that is sufficient for treating disorders, including obesity and obesity related disorders, and that would allow the skilled artisan to practice the instant invention without undue experimentation. The court has held that "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (*In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404 (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982)). One of ordinary skill in the art can readily identify the compounds useful in the methods of the present invention. As disclosed above, using the assays and criteria provided on pages 116 and 117 of the specification, one of ordinary skill in the art can readily determine if a compound is useful to treat obesity or an obesity related disorder. Applicants submit that a reasonable amount of guidance with respect to experimentation is given in the specification.

The Examiner stated that the specification has provided guidance for CB-1 binding assays to determine whether the compounds of the invention have an effect on the CB-1 receptor; however, the specification does not provide any working examples demonstrating the compounds treating obesity or guidance as to how to perform the claimed methods.

Applicants assert that in vitro and in vivo testing of each embodiment of the invention is not required under section 112, first paragraph. Applicants submit that section 112 does not require working examples (*In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (CCPA 1982)) and that the applicants' claim scope is not necessarily limited only to those embodiments actually disclosed in the specification (See *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also *Utter v. Hiraga*, 845 F.2d 998, 6 U.S.P.Q.2d at 1714 ("A specification may, within the meaning of 3 USC 112, first

paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses"), and that the embodiment need not necessarily have even been reduced to practice (See *In re Wright*, 999 F.2d 1557; 1561, 27 U.S.P.Q.2d 1510, 1513).

Applicants further submit that although the claimed invention has not yet been tested in human clinical trials for safety and effectiveness, such trials are not required to establish utility under the patent law:

Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating the incentive to pursue, through research and development, potential cures in many crucial areas...
In re Brana, 34 U.S. P.Q.2d 1436, 1442-3 (Fed Cir. 1995).

The Examiner indicated that the claims are drawn to a method of treating a disease mediated by the CB-1 receptor and obesity in humans. Thus the claims taken together with the specification imply that merely affecting the CB-1 receptor is sufficient to treat diseases which may be only peripherally related to the receptor's activity. The Examiner further stated that the state of the art in treating obesity with CB-1 antagonists is highly unpredictable. The teachings in Pagotto et al. (*Lancet*, 2005, v. 365, p. 1363-1364) describe the current state of the art as having a few existing drugs for the treatment of obesity and those only achieve a slight weight loss in the short term; and that the mechanism of pharmaceutical treatment of obesity has unknown modes of action.

Applicants respectfully disagree. The utility of using CB-1 antagonists to treat obesity was known before the October 30, 2003 priority date of the present application. Hildebrandt et al. disclose that their results support the hypothesis that chronic treatment of obese individuals with cannabinoid CB-1 receptor antagonists is a viable pharmacological approach to sustained weight loss (See enclosed reference: Hildebrandt et al., *European Journal of Pharmacology*, Vol. 462, pp. 125-132, February 2003). Additionally, the CB-1 antagonist, Rimonabant, was approved for the treatment of obesity in Europe on June 21, 2006, as described in the attached press release from Sanofi-Aventis. Rimonabant is currently marketed in Europe for treating obesity. Therefore it is not unpredictable that a CB-1 antagonist/inverse agonist, such as a compound of formula I, would be useful to treat obesity.

In summary, the instant specification provides a teaching of how to use the invention which would be credible to the person of ordinary skill in the art and which would permit the skilled artisan to use the claimed compositions for the stated utility without undue experimentation.

In view of the above arguments, Applicants respectfully submit that the rejection of Claim 16-19 is moot, that Claims 20 and new Claim 21 are adequately enabled and request reconsideration and withdrawal of the rejection of Claims 16-20 and new Claim 21 under 35 USC 112, first paragraph.

CLAIM OBJECTIONS

The Examiner indicated that Claims 1-10 and 16-20 are objected to for reading on non-elected subject matter.

Applicants have canceled Claim 3 and Claims 16-19.

Applicants have amended Claims 1, 2, 4, 5 and 9 to define R1 and R5 as hydrogen, R2 as -CH₃, Ar1 as phenyl, Ar2 as phenyl, Ar3 as phenyl and X as -CH₂- to comply with the restriction requirement that the Examiner has made final.

Applicants have amended Claim 8 to delete original compounds 21 and 49, wherein Ar3 is cyclohexyl to comply with the restriction requirement.

Applicants submit that Claims 2, 4, 5, 6, 7, 8, 10, 20 and 21 depend from Claim 1 or depend from a Claim that depends from Claim 1 and incorporate the amendments to Claim 1.

In view of the above amendments, Applicants respectfully submit that the rejection of Claims 3 and 16-19 is moot, that Claims 1, 2, 4-10, 20 and 21 read on elected subject matter, and request reconsideration and withdrawal of the objection to Claims 1, 2, 4-10, 20 and 21.

Applicants believe that all of the rejections have been overcome and therefore earnestly solicit an early Notice of Allowance.

Respectfully submitted,
By Baerbel R. Brown
Baerbel R. Brown, Reg. No. 47,449
Attorney for Applicants
MERCK & CO., Inc.
P.O. Box 2000
Tel: (732)594-0672

November 1, 2007



Antiobesity effects of chronic cannabinoid CB₁ receptor antagonist treatment in diet-induced obese mice

Audrey L. Hildebrandt, Dawn M. Kelly-Sullivan, Shawn C. Black*

Department of Cardiovascular and Metabolic Diseases, Pfizer Global Research and Development, Eastern Point Road, MS 8220-3119, Groton, CT 06340, USA

Received 7 November 2002; received in revised form 8 January 2003; accepted 14 January 2003

Abstract

We determined the effect of a cannabinoid CB₁ receptor antagonist (AM-251; *N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide) on food intake, body weight and adipose tissue mass in Western diet-induced obese (DIO) mice using a chronic, interrupted, oral dosing paradigm. The dosing paradigm was 2 weeks on treatment (treatment 1), 2 weeks off-treatment, followed by 2 weeks on treatment (treatment 2). During treatment 1 and treatment 2, food intake and body weight were reduced after a single dose. At 30 mg/kg/day, anorectic efficacy was maintained through 12 days (treatment 1) and 7 days (treatment 2). Body weight of AM-251-treated mice remained less than vehicle-treated mice throughout treatment 1 and treatment 2. Administration of AM-251 reduced inguinal subcutaneous, retroperitoneal and mesenteric adipose tissue mass. Antiobesity effects of AM-251 were lost during the off-treatment period, and hyperphagia was observed in treated animals. With re-initiation of AM-251 treatment, mice again responded to the effects of the compound. These results support the hypothesis that chronic treatment of obese individuals with cannabinoid CB₁ receptor antagonists is a viable pharmacologic approach to sustained weight loss.

© 2003 Elsevier Science B.V. All rights reserved.

Keywords: Anorectic; Cannabinoid; AM-251; Micro-CT; Obesity

1. Introduction

Obesity is increasingly recognized as a global health care problem epidemic in proportion (James et al., 2001). In the United States, where the epidemic is particularly evident, the number of approved drug treatments available to treat the disease has been reduced, rather than increased, over the last 5 years with the withdrawal of dexfenfluramine and fenfluramine. These two drugs were commonly prescribed and were associated with valvular heart disease (Connolly et al., 1997) which lead to their withdrawal. However, although the incidence of valvular heart disease was significantly higher in patients taking these drugs, it may not be as high as initially considered (Derry and Pritchard-Copley, 2002) and indeed in certain cases may spontaneously resolve over time (Vagelos et al., 2002). Nevertheless, current prescribed anti-obesity drug therapy is limited in the United States to orlistat (a

gastrointestinal lipase inhibitor) or sibutramine (an anorectic). Given the heterogeneity of the etiology of human obesity and limitations of currently available drugs (precluded concomitant use of sibutramine in hypertensive patients, for example), there is a therapeutic need for very safe and effective compounds to treat obesity (Van der Ploeg, 2000). In this respect, the endocannabinoid system has received significant attention for its potential for pharmacologic manipulation to treat obesity.

The endocannabinoid system comprises endogenous ligands (anandamide, 2-arachidonoyl glycerol, 2-arachidonoyl glyceryl ether (noladin ether), virodhamine) and two cannabinoid receptor subtypes (CB₁ and CB₂) (Hanus et al., 2001; Howlett et al., 2002; Porter et al., 2002). The cannabinoid CB₁ receptor is of interest with respect to appetite regulation. The exogenous agonist Δ^9 -tetrahydrocannabinol (the principal psychoactive component of marijuana) is hyperphagic in rodents (Williams et al., 1998) and man (Foltin et al., 1988). Experimental studies in rodents have also demonstrated hyperphagic effects of the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol (Williams and Kirkham, 1999). Further evidence that endogenous cannabinoids are

* Corresponding author. Tel.: +1-860-715-3817; fax: +1-860-715-7658.

E-mail address: shawn_c_black@groton.pfizer.com (S.C. Black).

involved in central nervous system control of appetite is derived from the observations that (i) direct administration of anandamide into the ventromedial hypothalamus (an area rich in cannabinoid CB₁ receptors) stimulates food intake (Jamshidi and Taylor, 2001), and (ii) concentrations of 2-arachidonoyl glycerol in the limbic forebrain and hypothalamus are positively correlated with stimulation of food intake in rats (Kirkham et al., 2002). Furthermore, following temporary food restriction, cannabinoid CB₁ receptor knockout mice eat less than their wild-type littermates, and cannabinoid CB₁ receptor antagonist treatment reduces food intake in wild-type but not knockout mice (Di-Marzo et al., 2001; Van der Ploeg, 2000). Thus, there is rationale to seek a cannabinoid CB₁ receptor antagonist as an antiobesity drug.

Discovery of the first selective cannabinoid CB₁ receptor antagonist was reported several years ago (Rinaldi-Carmona et al., 1994). This compound, SR141716A (*N*-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide), has subsequently been shown to have anorectic efficacy in a number of very short-term (acute) food intake studies in rats (Armone et al., 1997), mice (Di-Marzo et al., 2001) and monkeys (Simiand et al., 1998). These short-term studies investigated anorectic activity after a single dose of the compound. Two longer-term SR141716A efficacy studies in rats (Colombo et al., 1998) and mice (Ravinet et al., 2003) have shown the compound to be transiently anorectic but produce a sustained reduction in body weight compared to a control group.

To further investigate anorectic and weight loss pharmacology of cannabinoid CB₁ receptor antagonists, we used a clinically relevant administration route (oral) and a relevant Western diet-induced obese (DIO) mouse model. Furthermore, we investigated the chronic efficacy of a cannabinoid CB₁ receptor antagonist, AM-251, in mice using a chronic interrupted dosing paradigm. AM-251 (*N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide) is a structural analog to SR141716A differing by the halogen substitution of I for Cl. The interrupted dosing paradigm permitted efficacy assessment after a 2-week treatment period and then again after a 2-week off-treatment period. During the 2-week inter-treatment period, the appetitive behavioral response of mice after abrupt withdrawal of treatment was studied. Efficacy was determined by daily monitoring of food intake, body weight and, after each treatment period, adipose tissue mass. This study represents the first longer duration preclinical assessment of cannabinoid CB₁ receptor antagonist in an interrupted dosing paradigm.

2. Research methods and procedures

2.1. Animal care, handling and compound administration

All in vivo animal work conducted in this study conformed to the Guide for the Care and Use of Laboratory

Animals published by the Institute of Laboratory Animal Resources (National Research Council, 1996). Male C57BL/6 mice were obtained from Charles River (Wilmington, MA) and housed under standard conditions (12-h light/dark cycle, 22 °C). Animals were acclimated to single housing upon arrival, and fed a pelleted high fat diet (45% kcal from fat, D12451 Research Diets, New Brunswick, NJ). Prior to placement in the micro-CT instrument, mice were anesthetized with isoflurane. Anesthesia was maintained during the scanning procedure with 2% isoflurane and 2 l/min oxygen. Mice were continuously monitored during recovery from the anesthesia, before being returned to individual cage housing. For a period of 1 week prior to the baseline micro-CT scan, and before treatment period 1, all mice were acclimated to once daily dosing using 0.5% methylcellulose alone. Mice were administered AM-251 (purchased from Tocris Cookson, Ellisville, MO) via oral gavage at a dose of either 3 or 30 mg/kg/day in a suspension of 0.5% methylcellulose. The suspension was administered via a soft rubber cannula attached to a 1-ml syringe, at a dosing volume of 5 ml/kg. Compound was prepared fresh each day. All mice were administered AM-251 or vehicle alone 60 min before the onset of the dark cycle.

2.2. Food intake and body weight

Food intake and body weight were monitored daily. To measure food intake, the pelleted food was weighed and then placed in the cage food container; the food remaining 24 h later was weighed, and the difference represented the daily food intake. Animal weight and food weight were measured using an electronic scale. Unconsumed pelleted high fat food was discarded each day, and fresh, pelleted high fat diet provided to ensure consistent food quality was provided to the mice throughout the study. The high fat food was stored at 4 °C. A schematic of the experimental protocol is shown in Fig. 1.

2.3. Micro-CT scanning, image reconstruction and analysis

Images were obtained using a commercially available micro-CT system (MicroCAT®, ImTek, Oak Ridge, TN) with a high-resolution CCD/phosphor screen detector. The scanner consisted of a cylindrical diameter/long field view

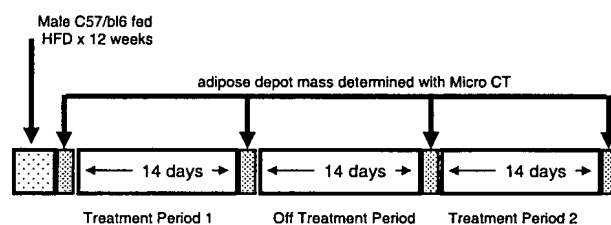


Fig. 1. Schematic representation of the protocol used to determine the effect of the CB₁ receptor antagonist AM-251 on food intake, body weight and adipose tissue depot mass in male, diet-induced obese C57BL/6 mice.

of 50 mm/50 mm with a spatial resolution of less than 50 μ m. The X-ray source was biased at 40 keV with the anode current set to 400 μ A. Anesthetized mice were placed on a radio-transparent mouse bed in a supine position, caudal end closest to the micro-CT with the rostral end held in place against an anesthesia delivery tube. The hind legs were moderately extended and held in place with clear tape to ensure a correct anatomical position (i.e. straight spine) and that the mouse position did not change once the scan procedure was initiated. An initial radiographic image was acquired at 90° to the plane of the mouse bed to allow correct positioning of the mouse by centering the scan acquisition area at the level of the iliac crest of each mouse. Image reconstruction, whereby a micro-CT scan of an individual mouse was manipulated to produce two-dimensional cross-sectional images, was performed using the MicroCAT® Reconstruction, Visualization, and Analysis Software (ImTek). Two sets of reconstructed images per scan were generated for each mouse for the determination of individual fat depot mass. User-defined placement of reconstruction slices were placed relative to defined anatomical sites (i.e. vertebral segments) (Hildebrandt et al., 2002). The first set of reconstructed images, consisting of six slices (intervertebral segments lumbar 6–7 through sacral 4–caudal 1), provided a montage for the analysis of inguinal and epididymal adipose tissue depots. The second reconstruction set, consisting of nine slices (intervertebral and midvertebral landmarks from lumbar 2–3 through lumbar 6–7) was used to define retroperitoneal and mesenteric adipose tissue depot masses. Reconstructed bitmap images were converted to TIFF (Tag Image File Format) images and subsequently analyzed for fat depot mass using Scion Image for Windows (Scion, Frederick MD).

2.4. Plasma insulin, leptin, cholesterol, glucose and triglyceride determinations

Plasma insulin and leptin were analyzed using commercially available ELISA kits designed for murine studies (Crystal Chem, Downers Grove, IL). To assay insulin concentrations, plasma samples were diluted 1:1 with buffer, and assayed according to the standard protocol in Crystal Chem Kit #INSSM021. Plasma leptin concentrations were analyzed in undiluted sample, according to the standard protocol of Crystal Chem Kit #90030. Plasma concentrations of glucose, cholesterol and triglyceride were analyzed using a Hitachi 912 Automatic Analyzer.

2.5. Statistical methods

All data shown are the mean \pm standard error of the mean (S.E.M.). The effects of time and dose on food intake, body weight or adipose depot mass of the groups studied (vehicle control, low dose AM-251 and high dose AM-251) were determined using a two-way analysis of variance with repeated measures analysis, followed by Newman–Keuls

test to determine where differences existed (if any) between the groups. Statistical comparisons of plasma insulin, leptin, cholesterol, glucose and triglyceride were done with a one-way analysis of variance, followed by Newman–Keuls test where appropriate. In all cases, differences were considered statistically different at $P < 0.05$.

3. Results

The effect of AM-251 on food intake during the first treatment period, the off-treatment period and the second treatment period is shown in Fig. 2(A–C). During the first

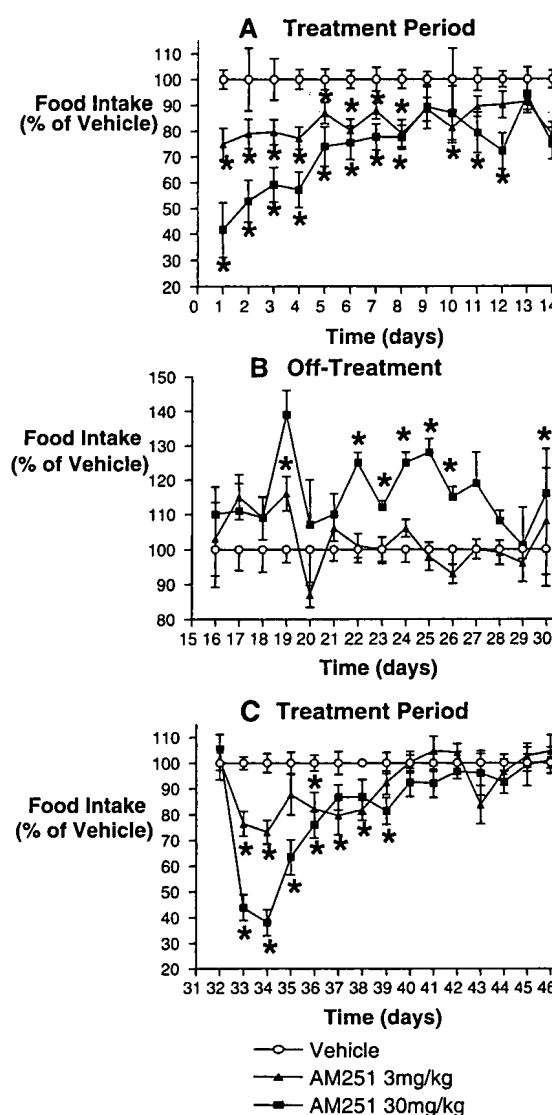


Fig. 2. Effect of AM-251 treatment on food intake (expressed as a percentage of mean vehicle-treated food intake) when administered at a dose of 3 or 30 mg/kg/day, during the three treatment periods studied. (A) Treatment period 1; (B) off-treatment period (no compound administered); (C) treatment period 2 (mice dosed as in treatment period 1). * $P < 0.05$ vs. vehicle. Error bars represent the S.E.M., with $n=10$ /group.

treatment period (Fig. 2A), there was an immediate and significant dose-dependent decrement in food intake in AM-251-treated male DIO mice. The anorectic effect of AM-251 waned over the 2-week treatment period; however, food intake remained significantly reduced through 8 days at the low dose (3 mg/kg/day) and through 12 days at the high dose (30 mg/kg/day). After withdrawal of either the low or high dose AM-251 treatment, there was a rapid return of food intake. In the high dose AM-251 group, as shown in Fig. 2B, there was a statistically significant hyperphagic response when administration of compound was stopped. The hyperphagia observed in the high dose group was statistically significant from days 7 through 11 of the off-treatment period. To determine if the mice treated with AM-251 remained responsive to the anorectic effect of the compound, treatment was re-initiated after 2 weeks off-treatment for another 2 weeks. As shown in Fig. 2C, there was again an immediate and statistically significant dose-dependent decrement in food intake in AM-251-treated mice. Similar to the dose-dependent responsiveness of the anorexia in the first treatment period, there was a waning of the compound's anorectic efficacy with time, with the low (3 mg/kg/day) dose efficacy waning more rapidly. Anorectic efficacy was observed for 4 and 7 days in the low dose and high dose AM-251-treated groups, respectively.

The results shown in Fig. 3 (panels A–C) indicate the effect of AM-251 treatment on body weight in the male DIO mice. The mean body weights of mice in the three groups were equivalent at the start of the study, as expected from the random assignment of mice to each group. The vehicle-treated control DIO mice continued to gain weight, at a slow rate, during treatment period 1. In contrast, DIO mice in the low dose (3 mg/kg/day) and high dose (30 mg/kg/day) AM-251-treated groups lost weight, in a dose-dependent fashion over the 2-week treatment period. There was a delay of 2–3 days before the weight loss was manifest; however, weight loss was sustained over the 2-week treatment period (Fig. 3A). During the off-treatment period (Fig. 3B), there were no significant increases in body weight of vehicle-treated mice. Not unexpectedly, considering the hyperphagia shown in Fig. 2B, there was a regain of body weight in both AM-251-treated groups during the off-treatment period. However, weight gain only brought the treated animals towards the vehicle-treated control group; hyperphagic mice did not overshoot the body weight of age-matched high fat diet fed controls. When the mice were dosed with AM-251 in treatment period 2 (Fig. 3C), there was again a dose-dependent reduction in weight that was sustained for the 2-week dosing period. The mice clearly remained sensitive to the weight loss effects of AM-251 when dosed at the low or high doses during treatment period 2.

The effect of AM-251 treatment on *in situ* adipose tissue mass in diet-induced obese mice is shown in Fig. 4A–D. At baseline, the mass of the four depots studied (inguinal subcutaneous, epididymal, retroperitoneal and mesenteric) were not different. There was no effect of the low dose AM-

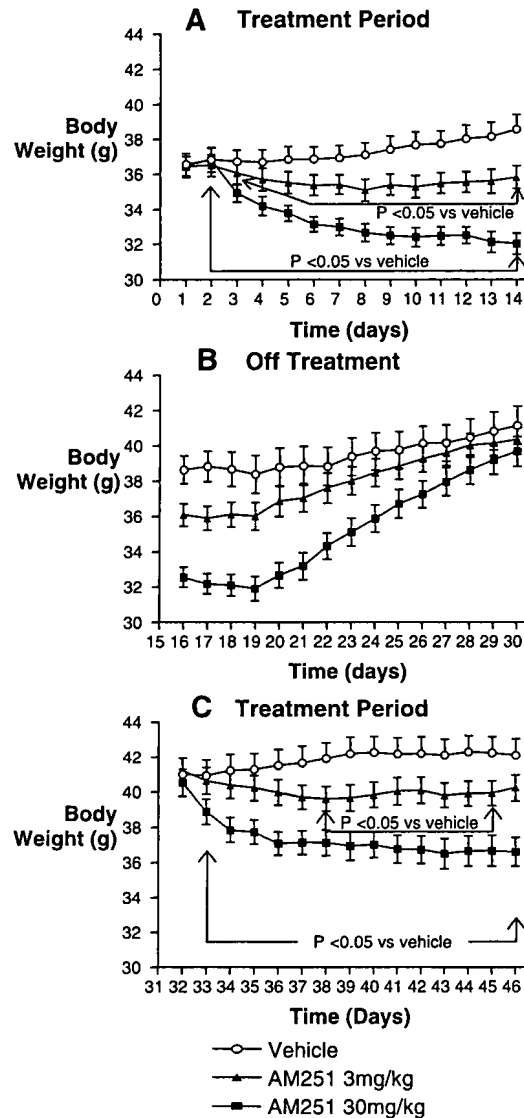


Fig. 3. Effect of AM-251 treatment on body weight when administered at a dose of 3 or 30 mg/kg/day, during the three treatment periods studied. (A) Treatment period 1; (B) off-treatment period (no compound administered); (C) treatment period 2 (mice dosed as in treatment period 1). Error bars represent the S.E.M., with $n=10$ /group.

251 treatment (3 mg/kg/day) on the mass of the adipose depots studied. Only the high dose AM-251 treatment (30 mg/kg/day) effected reductions in adipose depot mass. During treatment period 1, at the high dose of AM-251 (30 mg/kg/day), a general reduction in adipose tissue mass was observed. However, as shown in Fig. 4B, the epididymal adipose depot was resistant to AM-251 treatment, since there were no statistically significant effects of AM-251 on this depot after either treatment period 1 or 2. In the other depots (Fig. 4A,C,D), there was a significant reduction in adipose mass after treatment period 1 in high dose AM-251-treated mice (30 mg/kg/day). During the off-treatment period, adipose tissue mass of vehicle-treated mice was not consistently affected (i.e. there were no clear statistically

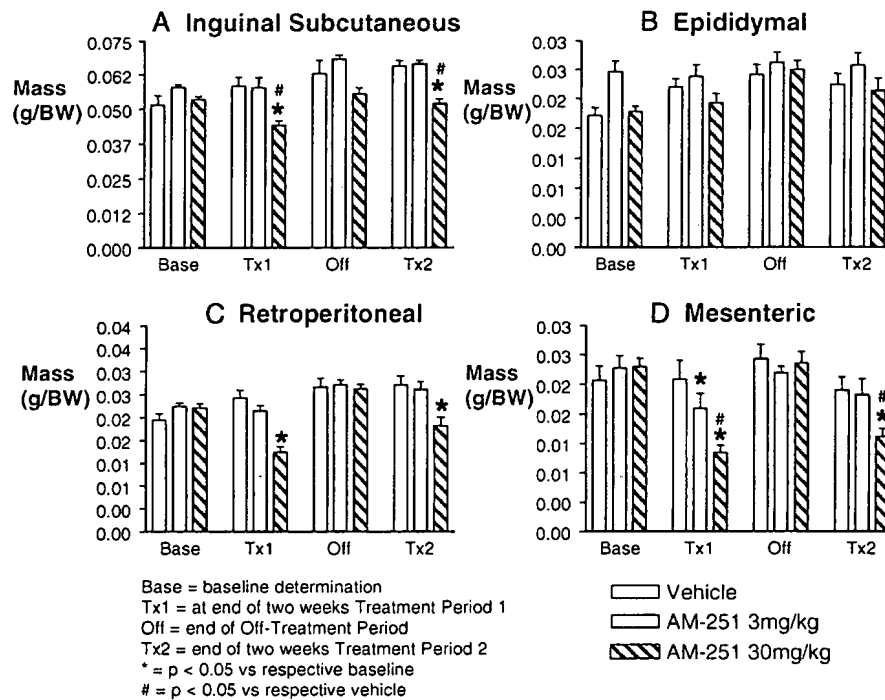


Fig. 4. Effect of AM-251 treatment on inguinal subcutaneous, epididymal, retroperitoneal and mesenteric adipose depot mass. Adipose depot mass was determined in situ with micro-CT technology at baseline (before any treatments initiated), at the end of 2-week treatment with AM-251 (treatment 1), at the end of 2-week off treatment (Off) and again after 2-week treatment with AM-251 (treatment 2). * $P < 0.05$ vs. respective baseline determination. # $P < 0.05$ vs. respective vehicle-treated group, i.e. within a treatment period. Error bars represent the S.E.M., with $n=6$ /group.

significant effects). However, there was a general trend in the vehicle-treated animals for adipose tissue to become greater with time. These effects are most likely related to the continued exposure and consumption of the mice to the highly palatable high fat diet. The adipose depot mass of mice that had been treated with high dose AM-251 increased to the level of the vehicle-treated group's during the "off-treatment" period. However, after treatment period 2, the same pattern of AM-251 treatment mediated reductions in adipose tissue mass were again evident (hatched bars of Fig. 4A,C,D).

The experiment terminated after the treatment period 2 adipose tissue micro-CT scans, and at that time, we obtained a plasma sample from the mice in each of the three groups studied and measured insulin, leptin, chole-

sterol, triglyceride and glucose concentrations. We did not obtain baseline, post-treatment period 1 or post-"off-treatment" samples since this may have compromised the status of the animals before starting the experiment, or midway through the experiment. As shown by the data in Table 1, there was no effect of 2 weeks daily treatment with AM-251 at a dose of 3 mg/kg/day on any of the parameters measured. At a dose of 30 mg/kg/day for 2 weeks, there was no effect of AM-251 treatment on plasma glucose or triglycerides. There was a 55% reduction in plasma insulin levels with high dose AM-251 treatment; however, the variability precluded this trend from being statistically significant from vehicle-treated mice. However, as shown in Table 1, 2 weeks of AM-251 treatment at a dose of 30 mg/kg/day lead to a significant reduction in plasma cholesterol (22% decrease) and leptin (29% decrease) concentrations.

Table 1
Plasma analyses after treatment period 2

	Leptin (pg/ml)	Insulin (pg/ml)	Glucose (mg/dl)	Cholesterol (mg/dl)	Triglycerides (mg/dl)
Vehicle	19.4±1.1	5.1±1.6	290±23	200±5	93±13
AM-251 (3 mg/kg)	19.7±1.7	4.5±1.5	315±31	192±4	98±15
AM-251 (30 mg/kg)	13.7±1.0*	2.3±1.1	315±13	157±3*	128±19

Values shown are the mean±S.E.M. ($n=9-10$ /group).

* Indicates a significant ($P < 0.05$) difference between vehicle- and AM-251-treated (30 mg/kg/day) group.

4. Discussion

The anorectic efficacy of the cannabinoid CB₁ receptor antagonist SR141716A is established (Arnone et al., 1997; Colombo et al., 1998; Di-Marzo et al., 2001; Ravinet et al., 2003; Simiand et al., 1998); however, anorectic effects of AM-251 have not been previously reported. Our current study sought to determine if AM-251 (different from SR141716A by virtue of a single halogen switch, I for Cl)

(Lan et al., 1999) demonstrated antiobesity efficacy in a chronic, interrupted dosing paradigm. AM-251 is a potent (a K_i value of 7.49 nM at cannabinoid CB₁ receptors) and selective (306-fold selective over CB₂) cannabinoid CB₁ receptor antagonist (Gatley et al., 1996, 1997). In vivo cannabinoid CB₁ receptor antagonist effects of AM-251 have been reported (Gardiner et al., 2002); however, this is the first report describing anorectic and weight loss effects of AM-251. Considering the in vitro pharmacologic profile of the compound, its structural similarity to SR141716A and the known pharmacology of that compound, efficacy was anticipated.

The principal novel aspect of this study was the chronic “on–off–on” treatment paradigm used to explore the anorectic/weight loss efficacy of the cannabinoid CB₁ receptor antagonist AM-251. Prior to this report, two studies reported on the anorectic efficacy of “chronic” cannabinoid CB₁ receptor antagonist treatment. The first study, of 2 weeks duration, demonstrated that in male non-obese Wistar rats SR141716A (10 mg/kg/day intraperitoneal administration) transiently inhibited food intake, with anorectic efficacy lost after 4 days treatment (Colombo et al., 1998). In the second study in male diet-induced obese mice, SR141716A (10 mg/kg/day administered orally) reduced energy intake by 48% after 1-week treatment. This anorectic effect waned over the subsequent 4-week treatment to a 12% decrease compared to vehicle-treated mice (Ravinet et al., 2003). However, the reduction in energy intake remained significant. Thus, these studies indicated that there was desensitization to the anorectic efficacy of cannabinoid CB₁ receptor antagonists, or at least SR141716A as it was the only compound studied, with “chronic” administration. In our study, also using a diet-induced obese male mouse model and using oral dosing, cannabinoid CB₁ receptor antagonist anorectic efficacy lasted for a period of 8 and 12 days during the first treatment period at 3 and 30 mg/kg/day, respectively. Our data and the data of Ravinet et al. (2003) show that under conditions of high fat diet-induced obesity, where energy intake is in excess of energy consumption, cannabinoid CB₁ receptor antagonists have a more sustained anorectic effect than in normal chow fed, growing rats. This may be of importance in consideration of the respective human population in which anorectic drug efficacy is, ultimately, sought.

A second major finding of this study was the weight loss efficacy of the cannabinoid CB₁ receptor antagonist AM-251. Similar to the anorectic efficacy discussed above, literature comparisons are restricted to the aforementioned normal, growing Wistar rat and diet-induced obese mouse studies (Colombo et al., 1998; Ravinet et al., 2003). In non-obese male Wistar rats, cannabinoid CB₁ receptor antagonist treatment significantly attenuated the rate of weight gain over a 2-week period (Colombo et al., 1998). In the 5-week diet-induced mouse study, weight loss efficacy was observed with SR141716A for a period of 5 weeks. The current study supports the weight loss efficacy of these two

previous studies; the high dose (30 mg/kg/day) and low dose (3 mg/kg/day) of AM-251 treatment lead to sustained reductions in body weight of male diet-induced obese mice. The significant reduction in body weight was observed both during treatment period 1, without prior exposure to the compound, and also during treatment period 2, after the mice had regained much of the weight previously lost during treatment period 1. It was interesting to note that although anorectic efficacy waned over time, during both treatment periods, the reduction in body weight was sustained. Therefore despite a waning of anorectic efficacy, cannabinoid CB₁ receptor antagonist treatment lead to a significant and sustained reduction in body weight. This is the primary goal of any therapeutic approach used to treat human obesity.

In designing this study, it was of particular interest to study not only the relative desensitization to anorectic effects that may occur with continued use of a cannabinoid CB₁ receptor antagonist in an obese mouse model, but also the effect of withdrawing the compound and then re-instituting treatment after a 2-week period. This approach has not been reported previously. It was interesting to observe that during the off-treatment period, in both low and high dose AM-251-treated groups, there was a return of treated animals' body weight to the vehicle-treated body weight range. During the 2-week off-treatment period, the high dose group of AM-251-treated mice exhibited hyperphagia. Although the mice in the high dose group consumed more food than vehicle controls during the 2-week off-treatment period, body weight did not exceed the vehicle group. This gain of body-weight was also similar to that observed in Wistar rats, although that study tracked food intake/body weight only for 1 week after treatment was terminated (Colombo et al., 1998). The implications of the observed hyperphagia remain speculative but in the mouse may include a physiological response to return body weight to a genetically determined “set-point” (Levin et al., 1997). It will be important to characterize any such response in humans treated with a cannabinoid CB₁ receptor antagonist. Possibly, tapering the drug administration over time may attenuate the hyperphagic response.

In this study we measured in situ, and longitudinally, the effect of cannabinoid CB₁ receptor antagonist treatment on adipose tissue depot mass using micro-CT technology. This technology affords the opportunity to measure adipose tissue mass in the same animal over time, and, in this experiment, in response to a drug treatment. The technology has recently been validated for the measurement of adipose tissue in mice (Hildebrandt et al., 2002). Administration of the high dose of AM-251 (30 mg/kg/day) reduced the mass of inguinal subcutaneous, retroperitoneal and mesenteric adipose tissue depots in DIO mice. The observed reductions in adipose tissue are in agreement with those previously observed with SR141716A treatment of diet-induced obese mice (Ravinet et al., 2003). Interestingly, epididymal adipose tissue was not responsive to cannabinoid CB₁ receptor

antagonist treatment; epididymal adipose depot mass did not change in response to AM-251 treatment either during treatment period 1 or treatment period 2. It was also observed in our studies that the high dose of AM-251 significantly reduced plasma leptin concentrations. The reduction in plasma leptin concentrations along with significant reductions in epididymal, inguinal subcutaneous and retroperitoneal adipose depot mass is in agreement with previous reports of the relationship between plasma leptin and the extent of adiposity in rodents and man (Maffei et al., 1995). It was also observed that here was a reduction in plasma total cholesterol in the high dose AM-251-treated group. Although this observation is of interest, as hypercholesterolemia is an independent risk factor for cardiovascular disease, the mechanism for this response remains to be determined.

There is an increasing body of evidence that the endocannabinoid system plays an important role in the regulation of appetitive behavior and, from a pharmacological point of view, that inhibition of the endocannabinoid system through antagonism of the cannabinoid CB₁ receptor may be an effective therapeutic approach to treating human obesity. Current preclinical evidence supports anorectic and weight loss efficacy through a 5-week period, and the current study extends our understanding in that efficacy was again clearly achievable after a 2-week “off-treatment” period; these data indicate tolerance or desensitization to the pharmacologic efficacy of cannabinoid CB₁ receptor antagonists may not limit their repetitive use in man. However, it is also apparent from these studies that during the “off-treatment” period, mice, which had the greater response to AM-251, also had a greater hyperphagia following cessation of treatment. This observed “rebound” of energy consumed may also be of relevance to the treatment of humans with this class of compounds. Whilst there is a growing body of preclinical evidence to support a role of the endocannabinoid system in control of appetitive behavior, and that cannabinoid CB₁ receptor antagonists may be an effective approach, ultimately data from clinical trials with novel cannabinoid CB₁ receptor antagonists will provide the key information as to the potential for this class of compounds to help treat the very serious epidemic of obesity.

References

- Arnone, M., Maruani, J., Chaperon, F., Thiebot, M.H., Poncelet, M., Soubrie, P., Le Fur, G., 1997. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB₁) receptors. *Psychopharmacology (Berl.)* 132, 104–106.
- Colombo, G., Agabio, R., Diaz, G., Lobina, C., Reali, R., Gessa, G.L., 1998. Appetite suppression and weight loss after the cannabinoid antagonist SR 141716. *Life Sci.* 63, L113–L117.
- Connolly, H.M., Crary, J.L., McGoon, M.D., Hensrud, D.D., Edwards, B.S., Edwards, W.D., Schaff, H.V., 1997. Valvular heart disease associated with fenfluramine–phentermine. *N. Engl. J. Med.* 337, 581–588.
- Derry, S., Pritchard-Copley, A., 2002. Appetite suppressants and valvular heart disease—a systematic review. *BMC Clin. Pharmacol.* 2, 6.
- Di-Marzo, V., Goparaju, S.K., Wang, L., Liu, J., Batkai, S., Jarai, Z., Fezza, F., Miura, G.I., Palmiter, R.D., Sugiura, T., Kunos, G., 2001. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature* 410, 822–825.
- Foltin, R.W., Fischman, M.W., Byrne, M.F., 1988. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11, 1–14.
- Gardiner, S.M., March, J.E., Kemp, P.A., Bennett, T., 2002. Complex regional haemodynamic effects of anandamide in conscious rats. *Br. J. Pharmacol.* 135, 1889–1896.
- Gatley, S.J., Gifford, A.N., Volkow, N.D., Lan, R., Makriyannis, A., 1996. 123I-labeled AM251: a radioiodinated ligand which binds in vivo to mouse brain cannabinoid CB₁ receptors. *Eur. J. Pharmacol.* 307, 331–338.
- Gatley, S.J., Lan, R., Pyatt, B., Gifford, A.N., Volkow, N.D., Makriyannis, A., 1997. Binding of the non-classical cannabinoid CP 55,940, and the diarylpyrazole AM251 to rodent brain cannabinoid receptors. *Life Sci.* 61, L-7.
- Hanus, L., Abu-Lafi, S., Fride, E., Breuer, A., Vogel, Z., Shalev, D.E., Kustanovich, I., Mechoulam, R., 2001. 2-Arachidonoyl glyceryl ether, an endogenous agonist of the cannabinoid CB₁ receptor. *Proc. Natl. Acad. Sci. U. S. A.* 98, 3662–3665.
- Hildebrandt, A.L., Kelly-Sullivan, D.M., Black, S.C., 2002. Validation of a high-resolution X-ray computed tomography system to measure murine adipose tissue depot mass in situ and longitudinally. *J. Pharmacol. Toxicol. Methods* 47, 99–106.
- Howlett, A.C., Barth, F., Bonner, T.I., Cabral, G., Casellas, P., Devane, W.A., Felder, C.C., Herkenham, M., Mackie, K., Martin, B.R., Mechoulam, R., Pertwee, R.G., 2002. International Union of Pharmacology: XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* 54, 161–202.
- James, P.T., Leach, R., Kalamara, E., Shayeghi, M., 2001. The worldwide obesity epidemic. *Obes. Res.* 9 (Suppl. 4), 228S–233S.
- Jamshidi, N., Taylor, D.A., 2001. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. *Br. J. Pharmacol.* 134, 1151–1154.
- Kirkham, T.C., Williams, C.M., Fezza, F., Di, M.V., 2002. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Br. J. Pharmacol.* 136, 550–557.
- Lan, R., Liu, Q., Fan, P., Lin, S., Fernando, S.R., McCallion, D., Pertwee, R., Makriyannis, A., 1999. Structure–activity relationships of pyrazole derivatives as cannabinoid receptor antagonists. *J. Med. Chem.* 42, 769–776.
- Levin, B.E., Dunn-Meynell, A.A., Balkan, B., Keeseey, R.E., 1997. Selective breeding for diet-induced obesity and resistance in Sprague–Dawley rats. *Am. J. Physiol.* 273, R725–R730.
- Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., 1995. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nat. Med.* 1, 1155–1161.
- Porter, A.C., Sauer, J.M., Knierman, M.D., Becker, G.W., Berna, M.J., Bao, J., Nomikos, G.G., Carter, P., Bymaster, F.P., Leese, A.B., Felder, C.C., 2002. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB₁ receptor. *J. Pharmacol. Exp. Ther.* 301, 1020–1024.
- Ravinet, T.C., Arnone, M., Delgorge, C., Gonalons, N., Keane, P., Maffrand, J.P., Soubrie, P., 2003. Anti-obesity effect of SR141716, a CB₁ receptor antagonist, in diet-induced obese mice. *Am. J. Physiol., Regul. Integr. Comp. Physiol.* 284, R345–R353.
- Rinaldi-Carmona, M., Barth, F., Heaulme, M., Shire, D., Calandra, B., Congy, C., Martinez, S., Maruani, J., Neliat, G., Caput, D., 1994. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett.* 350, 240–244.
- Simiand, J., Keane, M., Keane, P.E., Soubrie, P., 1998. SR 141716, a CB₁ cannabinoid receptor antagonist, selectively reduces sweet food intake in marmoset. *Behav. Pharmacol.* 9, 179–181.

- Vagelos, R., Jacobs, M., Popp, R.L., Liang, D., 2002. Reversal of Phen-Fen associated valvular regurgitation documented by serial echocardiography. *J. Am. Soc. Echocardiogr.* 15, 653–657.
- Van der Ploeg, L.H., 2000. Obesity: an epidemic in need of therapeutics. *Curr. Opin. Chem. Biol.* 4, 452–460.
- Williams, C.M., Kirkham, T.C., 1999. Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. *Psychopharmacology (Berl.)* 143, 315–317.
- Williams, C.M., Rogers, P.J., Kirkham, T.C., 1998. Hyperphagia in pre-fed rats following oral delta9-THC. *Physiol. Behav.* 65, 343–346.



sanofi aventis

Because health matters

ACOMPLIA® (RIMONABANT) RECEIVES MARKETING AUTHORISATION IN THE EUROPEAN UNION

***First-in-class CB₁ blocker approved for the treatment of obese patients,
or overweight patients with associated risk factors,
such as type 2 diabetes or dyslipidaemia***

Paris, France – June 21, 2006 – Sanofi-aventis announced today that the European Commission has granted marketing authorisation for ACOMPLIA® (rimonabant 20 mg/day) in all 25 European member states. ACOMPLIA®, discovered and developed by sanofi-aventis, is the first in a new class of drugs called CB₁ blockers. ACOMPLIA® is indicated as an adjunct to diet and exercise for the treatment of obese patients (BMI $\geq 30\text{kg/m}^2$), or overweight patients (BMI $>27\text{kg/m}^2$) with associated risk factors, such as type 2 diabetes or dyslipidaemia.

The marketing authorisation was based on the review of comprehensive efficacy and safety data, including data from the RIO clinical trial programme which involved more than 6,600 patients worldwide, of which over 4,500 were studied for up to two years. Results from the RIO programme demonstrated that one ACOMPLIA® 20 mg tablet taken every day significantly decreased weight and waist circumference, HbA_{1c}, and triglycerides and increased HDL-cholesterol levels. Importantly the label granted by the European Commission states that an estimated 50% of the observed improvements in HbA_{1c}, HDL-cholesterol and triglycerides were beyond that expected from weight loss alone.¹

“The approval of ACOMPLIA® in the European Union is important news for obese and overweight patients with additional cardiometabolic risk factors such as type 2 diabetes or dyslipidaemia who will now have access to an innovative treatment option,” said Jean-François Dehecq, Chairman and Chief Executive Officer of sanofi-aventis. *“Through our discovery, development and now this approval of ACOMPLIA®, sanofi-aventis has once again demonstrated our expertise and commitment to making first-in-class treatments available to patients and physicians alike.”*

ACOMPLIA® 20 mg is targeted at improving multiple cardiometabolic risk factors in obese and overweight patients. Those likely to gain most benefit will be patients presenting with abdominal obesity (a large waist circumference) who also have diabetes and/or dyslipidaemia. Almost half the adult population with a large waist circumference (defined as 102 cm/40 inches in men and 88cm/35 inches in women) present with at least 3 additional risk factors, all contributing to increased cardiometabolic risk.

Global cardiometabolic risk represents the overall risk of developing type 2 diabetes and/or cardiovascular disease and is due to a cluster of modifiable risk factors. Cardiometabolic risk factors include classical risk factors such as high LDL-cholesterol levels, hypertension and hyperglycaemia and emerging risk factors closely related to abdominal obesity (especially intra-abdominal adiposity), such as insulin resistance, low HDL-cholesterol, high triglyceride levels, and inflammatory markers such as adiponectin and CRP (C-reactive protein).

press release



sanofi aventis

Because health matters

press release

"Until now we have not had a medication that addresses the multiple cardiometabolic risk factors that put patients at risk for cardiovascular disease and type 2 diabetes," said Luc Van Gaal, M.D., Professor of Diabetology, Metabolism and Clinical Nutrition, Antwerp University Hospital, Belgium and Principal Investigator of the RIO Europe trial. "Rimonabant is an important advance to treat the multiple risk factors which contribute to the global risk for diabetes and cardiovascular disease, which will offer benefits beyond current treatments for individual risk factors such as blood pressure, cholesterol and diabetes."

ACOMPLIA® will be available in European Union countries for prescription as a 20 mg tablet to be taken once daily. The first launch of ACOMPLIA® will take place in the United Kingdom in July 2006 and will be followed by launches in Denmark, Ireland, Germany, Finland and Norway during the second half of 2006.

Safety and Tolerability

ACOMPLIA® 20mg has been evaluated for safety in over 6,300 patients. In placebo controlled studies the discontinuation rate due to adverse reactions was 15.7% for patients receiving ACOMPLIA®. The most common adverse events resulting in discontinuation were nausea, mood alteration with depressive disorders, anxiety and dizziness.¹

ACOMPLIA® should not be initiated in patients with hepatic or renal impairment or patients with uncontrolled serious psychiatric illnesses such as major depression.¹

About ACOMPLIA®

ACOMPLIA® works by selectively blocking CB₁ receptors found in the brain and in peripheral organs important in glucose and lipid (or fat) metabolism, including adipose tissue, the liver, gastrointestinal tract and muscle.² CB₁ receptor blockade with ACOMPLIA® acts to decrease the overactivity of the endocannabinoid system (EC system).^{3, 4} The EC system is a recently characterised physiological system that includes receptors such as the CB₁ receptor, and it is believed to play an important role in regulating body weight and in controlling energy balance, as well as glucose and lipid metabolism.⁵

About sanofi-aventis

Sanofi-aventis is the world's third largest pharmaceutical company, ranking number one in Europe. Backed by a world-class R&D organisation, sanofi-aventis is developing leading positions in seven major therapeutic areas: cardiovascular, thrombosis, oncology, metabolic diseases, central nervous system, internal medicine and vaccines. Sanofi-aventis is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

Forward Looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995. Forward-looking statements are statements that are not historical facts. These statements include financial projections and estimates and their underlying assumptions, statements regarding plans, objectives and expectations with respect to future events, operations, products and services, and statements regarding future performance. Forward-looking statements are generally



sanofi aventis

Because health matters

press release



identified by the words "expect," "anticipates," "believes," "intends," "estimates," "plans" and similar expressions. Although sanofi-aventis' management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in sanofi-aventis' annual report on Form 20-F for the year ended December 31, 2005. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.

References

¹ ACOMPLIA® Summary of Product Characteristics

² Pagotto U. Fighting obesity and associated risk factors by antagonising cannabinoid type 1 receptors. *Lancet*. 2005 Apr 16-22;365(9468):1363-64.

³ Van Gaal et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet*. 2005 Apr 16-22;365(9468):1389-97.

⁴ Di Marzo V, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature*. 2001;410:822-825.

⁵ Pagotto U. The Endocannabinoid System: A New Player in Reinforcement and Energy Control Functions. Poster presented at the Metabolic Syndrome, Type 2 Diabetes and Atherosclerosis Conference, Marrakech, 19 – 23 May 2004.